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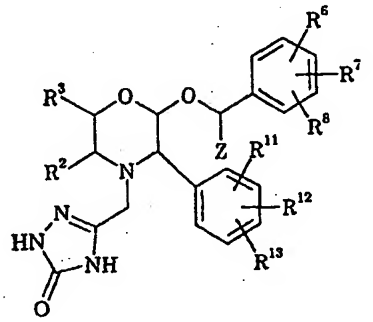
(54) Title: CHEMICAL SYNTHESIS OF MORPHOLINE DERIVATIVES



(I)

(57) Abstract

The present invention relates to a process for the preparation of mopholine derivatives of formula (I) which are useful as a therapeutic agents.

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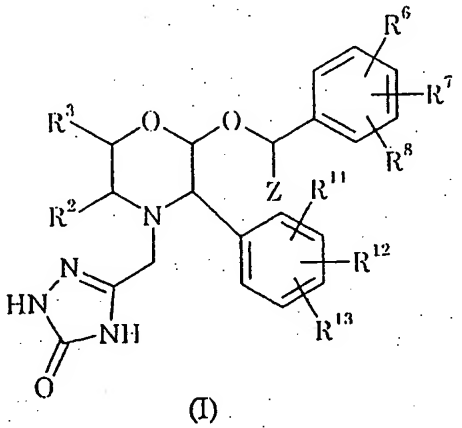
CHEMICAL SYNTHESIS OF MORPHOLINE DERIVATIVES

The present invention relates to a process for the preparation of morpholine derivatives, and in particular, the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, which are useful as therapeutic agents.

Compounds of formula (I), below, which are described in International patent specification No. WO 95/16679 (published 22nd June 1995), are potent and selective substance P (or neurokinin-1) receptor antagonists.



(I)

wherein

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) C_{2-6}alkenyl, and

(4) phenyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

(6) iodo, and

(7) $-CF_3$;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

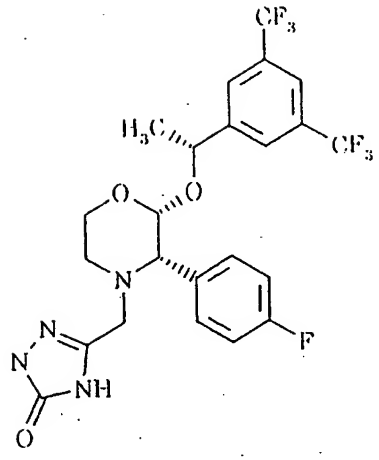
(6) iodo, and

(7) $-CF_3$; and

Z is C_{1-4}alkyl.

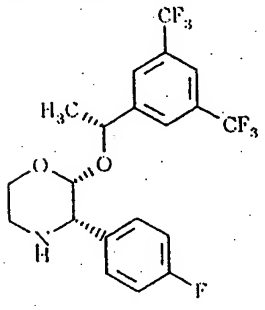
In particular, the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine has shown potential in the treatment of emesis, depression and anxiety. Substance P antagonists are also being investigated for other neuropsychiatric diseases, including bipolar disorder and schizophrenia, as well as postherpetic neuralgia and pain.

International patent specification No. WO 95/16679 describes the preparation of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine (hereinafter referred to as Compound A), which has the structure:

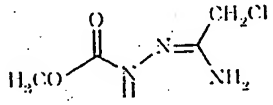


Compound A

by a two-step process starting from 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine. With reference to Examples 70 and 75 in WO 95/16679, Compound A is prepared as follows:

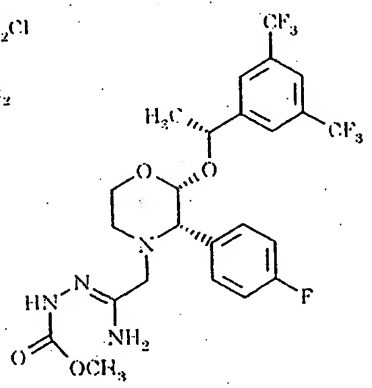


(from Ex. 74)

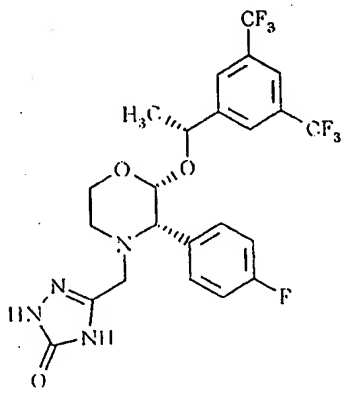


(from Ex. 45)

DEA, CH_3CN



xylenes, reflux

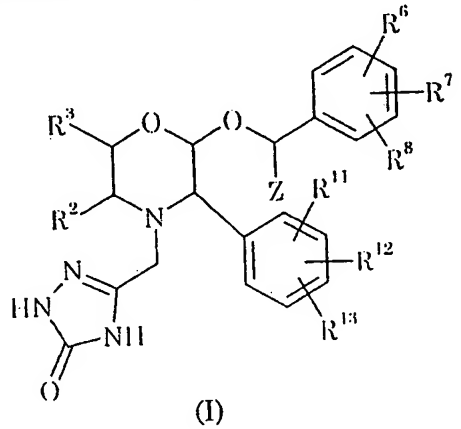


Compound A

This prior art process and in particular its requirement for a high temperature cyclisation step presents a number of practical difficulties which render it inconvenient when attempted on anything other than a relatively small scale. Therefore, there is a need for the development of a process which is readily amenable to scale-up and hence capable of practical application to the manufacturing plant.

The present invention accordingly provides a convenient, efficient process which utilizes a one-step alkylation with 3-chloromethyl-1,2,4-triazolin-5-one at ambient temperature that produces compounds of formula (I), and in particular Compound A, in a higher yield than the prior art two-step synthesis and which avoids a high temperature cyclisation. The novel process of the present invention is not only more energy efficient (since it requires no heating), but it is also more productive allowing for a shorter time-cycle on large scale and a higher operating concentration. The ability to effect the process of the present invention in one reaction vessel, in which the desired product crystallises from the reaction mixture at ambient temperature is a clear advantage over the prior art synthesis.

Thus, in a first aspect of the present invention, there is provided a process for the preparation of a compound of formula (I)



(I)

wherein

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) C_{2-6}alkenyl, and

(4) phenyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

(6) iodo, and

(7) $-CF_3$;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

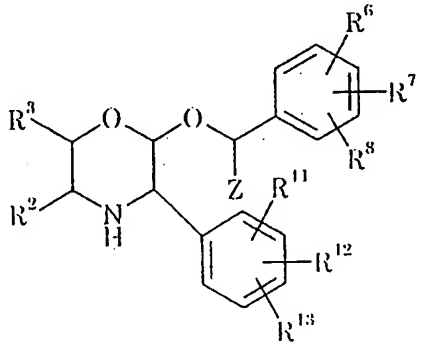
(6) iodo, and

(7) $-CF_3$; and

Z is C_{1-4}alkyl,

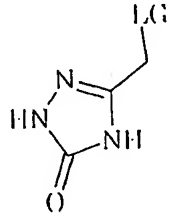
which comprises:

(i) reacting a compound of formula (II)



(II)

or a salt thereof, wherein R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13} and Z are as previously defined, with a compound of formula (III)



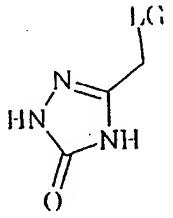
(III)

wherein LG is a leaving group selected from halogen (e.g. bromo, chloro or iodo) or an alkyl- or arylsulfonate group (e.g. mesylate or tosylate), in an organic solvent and in the presence of a base; and

(ii) collecting the resultant crystalline compound of formula (I).

In a particularly preferred aspect of the present invention, there is provided a process for the preparation of the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine which comprises:

(i) reacting 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine or a salt thereof, with a compound of formula (III)



(III)

as previously defined, in an organic solvent and in the presence of a base; and

(ii) collecting the resultant crystalline 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine.

In the compounds of formulae (I) and (II), preferably R^2 and R^3 are both independently hydrogen.

In the compounds of formulae (I) and (II), preferably R^6 and R^7 are independently selected from fluoro and $-CF_3$. In particular, R^6 and R^7 are both independently $-CF_3$.

In the compounds of formulae (I) and (II), preferably R^8 is hydrogen.

In the compounds of formulae (I) and (II), preferably R^{11} is hydrogen or fluoro.

In the compounds of formulae (I) and (II), preferably R^{12} and R^{13} are both independently hydrogen.

In the compounds of formulae (I) and (II), preferably Z is $-CH_3$.

In the compound of formula (III), preferably, the leaving group LG is chloro.

Suitable bases of use in the above reaction include organic bases or, more preferably, inorganic bases. Suitable organic bases include diisopropylethylamine or triethylamine. Suitable inorganic bases include sodium hydride or potassium carbonate.

Suitable organic solvents of use in the above reaction include dimethylformamide (especially where an inorganic base is used) and acetonitrile (especially where an organic base is used).

Most preferably, the above reaction is effected in dimethylformamide in the presence of potassium carbonate.

Conveniently, the above reaction is effected at room temperature.

Conveniently, the compound of formula (II), and in particular 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-morpholine, of use in step (i) of the above reaction is in the form of its free base. Preferably the compound of formula (II), and in particular 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-morpholine, of use in step (i) of the above reaction is in the form of its (*R*)-camphor sulfonic acid salt. More preferably, the compound of formula (II), and in particular 2-(*R*)-(1-(*R*)-(3,5-bis-(trifluoromethyl)phenyl)ethoxy)-3-

(*S*)-(4-fluorophenyl)morpholine. of use in step (i) of the above reaction is in the form of its *para*-toluenesulfonic acid salt.

According to a further or alternative aspect of the present invention, there is provided a process for the preparation of 3-chloromethyl-1,2,4-triazolin-5-one which comprises:

(i) treatment of semicarbazide hydrochloride with benyloxyacetyl chloride under Schotten-Baumann conditions to give benzyloxyacetylsemicarbazide;

(ii) cyclisation of the product of step (i) under basic conditions to give 3-benyloxymethyl-1,2,4-triazolin-5-one;

(iii) hydrogenation of the product of step (ii) to give 3-hydroxymethyl-1,2,4-triazolin-5-one; and

(iv) treatment of the product of step (iii) with a chlorinating agent to give 3-chloromethyl-1,2,4-triazolin-5-one.

According to yet a further or alternative aspect of the present invention, there is provided a process for the preparation of 3-hydroxymethyl-1,2,4-triazol-5-one which comprises steps (i) to (iii) as described above.

In step (i) above, the Schotten-Baumann conditions preferably involve use of aqueous alkali in a suitable solvent such as an ether, for example, tetrahydrofuran, at a reduced temperature, for example, between -10°C and +10°C, preferably 0°C. A particularly suitable aqueous alkali is aqueous sodium hydroxide.

In step (ii) above, cyclisation is preferably effected in the presence of a base such as an alkali metal hydroxide, for example, sodium hydroxide, at an elevated temperature, conveniently at reflux.

In step (iii) above, hydrogenation may be effected by catalytic hydrogenation using hydrogen in a suitable organic solvent such as an alcohol, for example, methanol, in the presence of a noble metal catalyst such as palladium or platinum or an oxide thereof on a support such as charcoal, and conveniently at room temperature and pressure. More

preferably, the hydrogenation is effected by transfer hydrogenation in a suitable organic solvent such as an alcohol, for example, methanol, using a hydrogenation catalyst, in particular, palladium on charcoal, in the presence of a hydrogen donor such as sodium hypophosphite, triethylammonium formate, potassium formate, ammonium formate or cyclohexene. Ammonium formate in water is especially preferred. The transfer hydrogenation is preferably effected at an elevated temperature, for example, between 50°C and 70°C, and preferably between 55°C and 60°C.

In step (iv) above, the chlorinating agent is, for example, an inorganic acid chloride such as $SOCl_2$, PCl_5, PCl_3 and $POCl_3$. Thionyl chloride ($SOCl_2$) is particularly preferred. The reaction is preferably effected in an organic solvent such as acetonitrile, conveniently at room temperature and pressure.

The following non-limiting examples illustrate processes according to the present invention:

EXAMPLE 1

Preparation of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine

A solution of 3-chloromethyl-1,2,4-triazolin-5-one (3.18 g) in DMF (30 ml) was added over 1 hour to a slurry of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine (R)-camphor sulfonic acid salt (15 g) and potassium carbonate (7.71 g) in DMF (100 ml) at 22°C. The reaction mixture was aged at 22°C for 20 minutes, then water (400 ml) was added over 30 minutes. The crystallising mixture was cooled in an ice bath, aged for 30 minutes and the product collected by filtration. The solid title compound was washed with water (400 ml), air dried and dried *in vacuo* at 45-50°C. Yield = 11.4 g; 98.1% HPLC w/w assay; 93.2% assay yield; (97.1A% HPLC profile).

EXAMPLE 2

Steps (i) and (ii) Preparation of 3-benzyloxymethyl-1,2,4-triazolin-5-one

Sodium hydroxide pellets (10.83 g) were added to a cold (0°C), vigorously stirred, solution of semicarbazide hydrochloride (15.1 g) in water (10 ml)/THF (50 ml) under a nitrogen atmosphere. A solution of benzyloxyacetyl chloride (25 g) in THF (100 ml) was added over five minutes and the mixture aged at 0°C for 2 hours (reaction complete by HPLC).

THF was removed under reduced pressure, 2M sodium hydroxide (60 ml) was added and the solution heated to reflux temperature for 5 hours. The reaction mixture was cooled to room temperature and left to stand for 18 hours. The solution was neutralised with 6M hydrochloric acid and the slurry cooled in an ice-bath for 1 hour. The product was collected by filtration, washed with cold water (10 ml) and dried *in vacuo*. 3-Benzyloxy-methyl-1,2,4-triazolin-5-one (16.7 g) was obtained in 60% yield as a white crystalline solid. mp. 190-192°C; ^{1}H NMR in d_6 DMSO δ=4.20 (2H, s, PhC$\underline{H}_2$), 4.42 (2H, s, OC$\underline{H}_2$=N), 7.25 (5H, s, Ph), 11.34 (1H, s, N$\underline{H}$) and 11.50 (1H, s, N$\underline{H}$) ppm and ^{13}C NMR in d_6 DMSO, δ=64.1 (O$\underline{C}$H$_2$C=N), 72.4 (Ph$\underline{C}$H$_2$O), 128.5 (Ph), 128.6 (Ph), 129.1 (Ph), 138.5 (Ph), 145.4 ($\underline{C}$=N) and 157.1 (NH$\underline{C}$ONH) ppm; mass spectroscopy M+H = 206, M+NH$_4$ = 223.

Step (iii) Preparation of 3-hydroxymethyl-1,2,4-triazolin-5-one

3-Benzyloxymethyl-1,2,4-triazolin-5-one (31g) and 10% palladium on charcoal (3.1 g) were slurried in methanol (200 ml), under a nitrogen atmosphere. A solution of ammonium formate (47.7 g) in water (20 ml) was added and the mixture was vigorously stirred and heated to 55-60°C. 10% Palladium on charcoal (3.1 g) was added after 2 hours and at 3 hours catalyst (1.55 g) and ammonium formate (9.5 g) in water (4 ml) were

charged. After 4 hours the reaction mixture was cooled to room temperature and left to stand overnight. The methanol solution was evaporated, under reduced pressure, to low volume and flushed by continuous addition of methanol (3L), at 50-55°C, to remove the excesss ammonium formate. The hot mixture was filtered through solka floc (15 g), the filtrate concentrated to low volume and solvent switched to acetonitrile (2 x 400 ml). The slurry was concentrated to about 100 ml, the product collected by filtration and then dried *in vacuo*. 3-Hydroxymethyl-1,2,4-triazolin-5-one (17.1 g) was obtained in 98.3% yield mp. 187-189°C (Lit = 187°C); ^{1}H NMR in d_6 DMSO δ= 4.34 (2H, s, HOC<u>H</u>$_2$) and 11.42 (2H, bs N<u>H</u>) ppm and ^{13}C NMR in d_6 DMSO δ=56.3 (HO<u>C</u>H$_2$), 148.5 (CH$_2$<u>C</u>=N) and 157.1 (NH<u>C</u>ONH) ppm; mass spectroscopy M+H=116, M+NH$_4$=133.

EXAMPLE 3

Preparation of 3-Chloromethyl-1,2,4-triazolin-5-one

Thionyl chloride (19.9 g) was added, over five minutes, to a slurry of 3-hydroxymethyl-1,2,4-triazolin-5-one (17 g) in acetonitrile (170 ml) at 20°C under a nitrogen atmosphere. The reaction mixture was aged at 20°C for 18 hours. [Note: after 30 minutes all the starting material had dissolved. At 1 hour the product began to crystallise]. TLC analysis (SiO_2; ethyl acetate/methanol (9/1); I_2) indicated that the reaction was complete. Hexane (510 ml) was added in one portion, the reaction cooled in an ice bath for 1 hour and the product collected by filtration. The solid was washed with hexane (100 ml) and dried *in vacuo*. 3-Chloromethyl-1,2,4-triazolin-5-one (17.2 g) was obtained as a white solid in 87.4% yield. mp 197-199°C; ^{1}H NMR in d_6 DMSO δ= 4.43 (2H, s, C<u>H</u>$_2$), 11.48 (1H, s, N<u>H</u>) and 11.64 (1H, s, N<u>H</u>) ppm and ^{13}C NMR in d_6 DMSO, δ=37.0 (Cl<u>C</u>H$_2$), 144.4 (CH$_2$<u>C</u>=N) and 156.8 (NH<u>C</u>ONH) ppm.

EXAMPLE 4

Alternative Preparation of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)-ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine

(1) Alternative Method using N,N-diisopropylethylamine/DMF

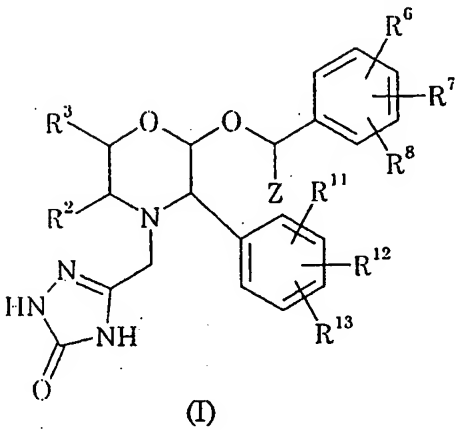
A solution of 3-chloromethyl-1,2,4-triazolin-5-one (2.56 g) in DMF (20 ml) was added over 1 hour to a slurry of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine *para*-toluenesulfonic acid salt (12 g) and N,N-diisopropylethylamine (5.15 g) in DMF (40 ml) at 21°C. The reaction was aged at 21-23°C for 30 minutes, then water (120 ml) was added over 20 minutes. The crystallising mixture was cooled in an ice bath, aged for 30 minutes and the product collected by filtration. The solid title compound was washed with water (96 ml), air dried and dried *in vacuo* at 50°C. Yield = 9.65 g; 99.7% isolated yield.

(2) Alternative Method using potassium carbonate/DMF

A solution of 3-chloromethyl-1,2,4-triazolin-5-one (1.40 g) in DMF (13.5 ml) was added over 1 hour to a slurry of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine *para*-toluenesulfonic acid salt (6.77 g) and potassium carbonate (1.55 g) in DMF (27 ml) at 19°C. The reaction was aged at 19-21°C for 30 minutes, then water (81 ml) was added over 20 minutes. The crystallising mixture was cooled in an ice bath, aged for 30 minutes and the product collected by filtration. The solid title compound was washed with water (54 ml), air dried and dried *in vacuo* at 50°C. Yield = 5.37 g; 98.0% HPLC w/w assay; 96.4% assay yield.

CLAIMS:

1. A process for the preparation of a compound of formula (I)



(I)

wherein

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) C_{2-6}alkenyl, and

(4) phenyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

(6) iodo, and

(7) $-CF_3$;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

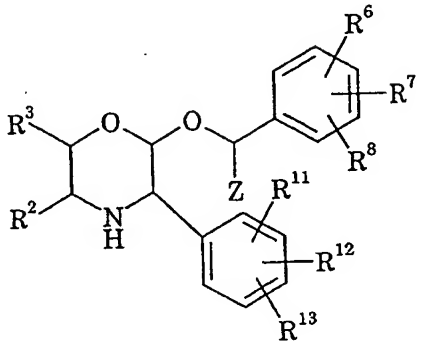
(6) iodo, and

(7) $-CF_3$; and

Z is C_{1-4}alkyl,

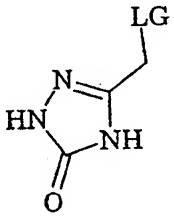
which comprises:

(i) reacting a compound of formula (II)



(II)

or a salt thereof, wherein R^2, R^3, R^6, R^7, R^8, R^{11}, R^{12}, R^{13} and Z are as previously defined, with a compound of formula (III)



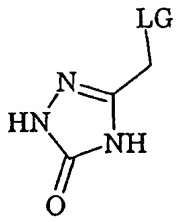
(III)

wherein LG is a leaving group selected from halogen (e.g. bromo, chloro or iodo) or an alkyl- or arylsulfonate group (e.g. mesylate or tosylate), in an organic solvent and in the presence of a base; and

(ii) collecting the resultant crystalline compound of formula (I).

2. A process for the preparation of the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine which comprises:

(i) reacting 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine or a salt thereof, with a compound of formula (III)



(III)

as defined in Claim 1, in an organic solvent and in the presence of a base; and

(ii) collecting the resultant crystalline 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine.

3. A process according to Claim 1 or Claim 2 wherein the leaving group LG is chloro.

4. A process according to Claim 1 or Claim 2 wherein the base is an organic base.

5. A process according to Claim 4 wherein the organic base is selected from diisopropylethylamine or triethylamine.

6. A process according to Claim 1 or Claim 2 wherein the base is an inorganic base.

7. A process according to Claim 6 wherein the inorganic base is selected from sodium hydride or potassium carbonate.

8. A process according to any one of Claims 1 to 5 wherein the organic solvent is acetonitrile.

9. A process according to any one of Claims 1 to 3, 6 or 7 wherein the organic solvent is dimethylformamide.

10. A process according to Claim 1 or Claim 2 wherein step (i) is effected in dimethylformamide in the presence of potassium carbonate.

11. A process according to any one of Claims 1 to 10 wherein the reaction is effected at room temperature.

12. A process according to any one of Claims 2 to 11 wherein the 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine of use in step (i) is in the form of its free base or its (*R*)-camphor sulfonic acid salt or its *para*-toluenesulfonic acid salt.

13. A process for the preparation of 3-chloromethyl-1,2,4-triazolin-5-one which comprises:

(i) treatment of semicarbazide hydrochloride with benyloxyacetyl chloride under Schotten-Baumann conditions to give benzyloxyacetylsemicarbazide;

(ii) cyclisation of the product of step (i) under basic conditions to give 3-benyloxymethyl-1,2,4-triazolin-5-one;

(iii) hydrogenation of the product of step (ii) to give 3-hydroxymethyl-1,2,4-triazolin-5-one; and

(iv) treatment of the product of step (iii) with a chlorinating agent to give 3-chloromethyl-1,2,4-triazolin-5-one.

14. A process for the preparation of 3-hydroxymethyl-1,2,4-triazol-5-one which comprises

(i) treatment of semicarbazide hydrochloride with benyloxyacetyl chloride under Schotten-Baumann conditions to give benzyloxyacetylsemicarbazide;

(ii) cyclisation of the product of step (i) under basic conditions to give 3-benyloxymethyl-1,2,4-triazolin-5-one; and

(iii) hydrogenation of the product of step (ii) to give 3-hydroxymethyl-1,2,4-triazolin-5-one.

15. A process according to Claim 13 or 14 wherein, in step (i), the Schotten-Baumann conditions involve use of aqueous alkali in an ether, at a reduced temperature.

16. A process according to Claim 15 wherein the aqueous alkali is aqueous sodium hydroxide.

17. A process according to Claim 15 or 16 wherein the ether is tetrahydrofuran.

18. A process according to any one of Claims 15 to 17 wherein the Schotten Baumann reaction is effected between -10°C and +10°C.

19. A process according to Claim 13 or 14 wherein, in step (ii), cyclisation is effected in the presence of a base at an elevated temperature.

20. A process according to Claim 19 wherein the base is an alkali metal hydroxide.

21. A process according to Claim 20 wherein the alkali metal hydroxide is sodium hydroxide.

22. A process according to any one of Claims 19 to 21 wherein the reaction is effected at reflux.

23. A process according to Claim 13 or 14 wherein, in step (iii), hydrogenation is effected by catalytic hydrogenation using hydrogen in an organic solvent, and in the presence of a noble metal catalyst on a support.

24. A process according to Claim 23 wherein the organic solvent is an alcohol.

25. A process according to Claim 24 wherein the alcohol is methanol.

26. A process according to any one of Claims 23 to 25 wherein the noble metal catalyst is palladium or platinum or an oxide thereof.

27. A process according to any one of Claims 23 to 26 wherein the support is charcoal.

28. A process according to any one of Claims 23 to 27 wherein the reaction is effected at room temperature and pressure.

29. A process according to Claim 13 or 14 wherein, in step (iii), hydrogenation is effected by transfer hydrogenation in a organic solvent using a hydrogenation catalyst in the presence of a hydrogen donor.

30. A process according to Claim 29 wherein the organic solvent is an alcohol.

31. A process according to Claim 30 wherein the alcohol is methanol.

32. A process according to any one of Claims 29 to 31 wherein the hydrogenation catalyst is palladium on charcoal.

33. A process according to any one of Claims 29 to 32 wherein the hydrogen donor is selected from sodium hypophosphite, triethylammonium formate, potassium formate, ammonium formate and cyclohexene.

34. A process according to Claim 33 wherein the hydrogen donor is ammonium formate in water.

35. A process according to any one of Claims 29 to 34 wherein the transfer hydrogenation is effected at an elevated temperature.

36. A process according to Claim 35 wherein the reaction is effected at a temperature between 50°C and 70°C.

37. A process according to Claim 13 wherein, in step (iv), the chlorinating agent is an inorganic acid chloride.

38. A process according to Claim 37 wherein the inorganic acid chloride is selected from $SOCl_2$, PCl_5, PCl_3 and $POCl_3$.

39. A process according to Claims 37 or 38 wherein the reaction is preferably effected in an organic solvent.

40. A process according to Claim 39 wherein the organic solvent is acetonitrile.

41. A process according to any one of Claims 37 to 40 wherein the reaction is effected at room temperature and pressure.

INTERNATIONAL SEARCH REPORT

International Application No
PC./GB 99/01842

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/06 C07D249/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 1999	17/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

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Inte tion.. plication No
PC1/GB 99/01842

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